

# PATENT COOPERATION TREATY

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From the  
 INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

## PCT

To:

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RECEIVED

17 JAN 2005

BOULT WADE  
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### NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing  
 (day/month/year)

14.01.2005

Applicant's or agent's file reference  
 CDM/P61500/001

### IMPORTANT NOTIFICATION

International application No.  
 PCT/GB 03/03686

International filing date (day/month/year)  
 22.08.2003

Priority date (day/month/year)  
 23.08.2002

Applicant  
 SOLEXA LIMITED

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

#### 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international  
 preliminary examining authority:



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# PATENT COOPERATION TREATY

## PCT



### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

|   |   |  |
|---|---|--|
| Applicant's or agent's file reference<br><b>CDM/P61500/001</b>  | <b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |  |
| International application No.<br><b>PCT/GB 03/03686</b>   | International filing date ( <i>day/month/year</i> )<br><b>22.08.2003</b>  | Priority date ( <i>day/month/year</i> )<br><b>23.08.2002</b> |
| International Patent Classification (IPC) or both national classification and IPC<br><b>C07H21/00</b> |   |  |
| Applicant<br><b>SOLEXA LIMITED</b>  |   |  |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:
- I ☒ Basis of the opinion
  - II ☐ Priority
  - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☐ Lack of unity of invention
  - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI ☐ Certain documents cited
  - VII ☐ Certain defects in the international application
  - VIII ☐ Certain observations on the international application

|   |   |
|---|---|
| Date of submission of the demand<br><br><b>11.03.2004</b>   | Date of completion of this report<br><br><b>14.01.2005</b>  |
| Name and mailing address of the international preliminary examining authority:<br> European Patent Office - P.B. 5818 Patentlaan 2<br>NL-2280 HV Rijswijk - Pays Bas<br>Tel. +31 70 340 - 2040 Tx: 31 651 epo nl<br>Fax: +31 70 340 - 3016 | Authorized Officer<br><br><b>de Nooy, A</b><br><br>Telephone No. +31 70 340-2338<br> |

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB 03/03686

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, Pages**

1-116 as originally filed

**Claims, Numbers**

1-50 as originally filed

**Claims, Pages**

117, 118 received on 23.11.2004 with letter of 23.11.2004

**Drawings, Sheets**

1-7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB 03/03686

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-2 (in part), 3-4 (in full), 5-11 (in part), 12-28 (in full), 29-50 (in part)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-2 (in part), 3-4 (in full), 5-11 (in part), 12-28 (in full), 29-50 (in part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

|                               |             |                                   |
|-------------------------------|-------------|-----------------------------------|
| Novelty (N)                   | Yes: Claims | 1-2, 5-11, 29-50                  |
|                               | No: Claims  |                                   |
| Inventive step (IS)           | Yes: Claims | 2, 8, 11, 31-33, 37-39            |
|                               | No: Claims  | 1, 5-7, 9-10, 29-30, 34-36, 40-50 |
| Industrial applicability (IA) | Yes: Claims | 1-2, 5-11, 29-50                  |
|                               | No: Claims  |                                   |

2. Citations and explanations

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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. **PCT/GB 03/03686**

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**see separate sheet**

**Re Item III**

Note that this examination is only for claims 1-2, 5-11, 29-50 (all in part) for which the modified nucleotide or nucleoside is as claimed in claim 1 where Z is -CR4(R5)-O-CR4(R5)-O-R6 or -CR4(R5)-O-CR4(R5)-S-R6 with R4, R5 and R6 as in Figure 3 (as filed with the letter of 23 November 2004; note that the other amendments of claim 1 in this letter are not examined here since they have not been searched), and methods and kits pertaining thereto, since no search report was established for the other parts of the claims.

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following document:

D1: WO0229003

**Novelty**

The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1-2, 5-11, 29-50 is new in the sense of Article 33(2) PCT. In the prior art no document is disclosed containing nucleosides or nucleotides having an -CR4(R5)-O-CR4(R5)-O-R6 or -CR4(R5)-O-CR4(R5)-S-R6 3'-O protecting group with R4, R5 and R6 as in Figure 3.

**Inventive step**

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 5-7, 9-10, 29-30, 34-36, 40-50 does not involve an inventive step in the sense of Article 33(3) PCT.

The document D1 is regarded as being the closest prior art to the subject-matter of claims 1, 5-7, 9-10, 29-30, 34-36, 40-50 and discloses modified nucleosides for use in sequencing reactions using polymerases. The subject matter of those claims differs from D1 in that instead of the -CH2-O-CH3 protecting group of D1 (see figures and claims), -CR4(R5)-O-CR4(R5)-O-R6 or -CR4(R5)-O-CR4(R5)-S-R6 as protecting groups with R4, R5 and R6 as in Figure 3 are claimed.

The problem to be solved by the present invention may therefore be regarded as provision of a further compounds for use in a sequencing reaction.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. . PCT/GB 03/03686

The solution proposed in claims 1, 5-7, 9-10, 29-30, 34-36, 40-50 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

In order to solve the above problem, the skilled man would look for other protection-deprotection strategies. Having knowledge of D1, the skilled man would modify the protective group by adding a substitution in the form of an -O-R6 or -S-R6. In order to contain an inventive step, the applicant should show that those different protecting groups have an advantage over the ones of D1.

10/525401

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DT01 Rec'd PCT/PTC 2.3 FEB 2005

## CLAIMS

1. A modified nucleotide or nucleoside molecule comprising a purine or pyrimidine base and a ribose or deoxyribose sugar moiety having a removable 3'-OH blocking group covalently attached thereto, such that the 3' carbon atom has attached a group of the structure

-O-Z

- wherein Z is any of  $-C(R^{IV})_2-O-R''$ ,  $-C(R')_2-N(R'')_2$ ,  $-C(R')_2-N(H)R''$ ,  $-C(R^{IV})_2-S-R''$  and  $-C(R')_2-F$ ,

wherein  $-C(R^{IV})_2-O-R''$  is of the formula  $-CR^4(R^5)-O-CR^4(R^5)-OR^6$  or of the formula  $-CR^4(R^5)-O-CR^4(R^5)-SR^6$ ; and wherein  $-C(R^{IV})_2-S-R''$  is of the formula  $-CR^4(R^5)-S-CR^4(R^5)-OR^6$  or of the formula  $-CR^4(R^5)-S-CR^4(R^5)-SR^6$ ;

- wherein each  $R''$  is or is part of a removable protecting group;

each  $R'$  is independently a hydrogen atom, an alkyl, substituted alkyl, arylalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclic, acyl, cyano, alkoxy, aryloxy, heteroaryloxy or amido group, or a detectable label attached through a linking group; or  $(R')_2$  represents an alkylidene group of formula  $=C(R''')_2$  wherein each  $R'''$  may be the same or different and is selected from the group comprising hydrogen and halogen atoms and alkyl groups;

- each  $R^4$  and  $R^5$  is independently a hydrogen atom or an alkyl group;

$R^6$  is alkyl, cycloalkyl, alkenyl, cycloalkenyl or benzyl; and

- wherein said molecule may be reacted to yield an intermediate in which each  $R''$  is exchanged for H or, where Z is  $-C(R')_2-F$ , the F is exchanged for OH, SH or  $NH_2$ , preferably OH, which intermediate dissociates under aqueous conditions to afford a molecule with a free 3'OH; with the proviso that where Z is  $-C(R^{IV})_2-S-R''$ , both  $R^{IV}$  groups are not H.

2. A molecule according to claim 1 wherein  $R'$  is an alkyl or substituted alkyl.



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3. A molecule according to claim 1 or claim 2  
wherein -Z is of formula  $-C(R')_2-N_3$ .

4. A molecule according to any one of claims 1 to 3  
5 wherein Z is an azidomethyl group.

5. A molecule according to claim 1 or claim 2  
wherein R" is a benzyl or substituted benzyl group.

10 6. A molecule according to any preceding claim  
wherein said base is linked to a detectable label via  
a cleavable linker or a non-cleavable linker.

15 7. A molecule according to claim 6 wherein said  
linker is cleavable.

20 8. A molecule according to any one of claims 1 to 5  
wherein a detectable label is linked to the molecule  
through the blocking group by a cleavable or non-  
cleavable linker.

9. A molecule according to any one of claims 6 to 8  
wherein said detectable label is a fluorophore.

25 10. A molecule according to any one of claims 6 to 9  
wherein said linker is acid labile, photolabile or  
contains a disulfide linkage.

30 11. A modified nucleotide molecule as claimed in any  
one of claims 1 to 10 which comprises one or more  $^{32}P$   
atoms in its phosphate portion.

12. A nucleoside, nucleotide or polynucleotide